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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE US PATENT APPLICATION OF
YIQING ZOU ET AL.

SERIAL NO. 08/216,440

FILED: March 23, 1994

FOR: ANTIMALARIAL COMPOSITIONS

Commissioner of Patents and Trademarks
Washington D.C. 20231 USA

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DECLARATION OF WALTHER H. WERNSDORFER

I, Walther H. Wernsdorfer, citizen of the Federal Republic of Germany and resident of Vienna, Austria, do hereby declare and say as follows:

That I am a Graduate of The Friedrich Alexander University of Erlangen, Federal Republic of Germany, where I graduated in 1952 and obtained the approbation in medicine (M.B.B.S);

That I am a Graduate of The Ludwig Maximilian University of Munich, Federal Republic of Germany, where I graduated in 1953 and obtained the Degree of a Doctor of Medicine (M.D.);

That I have undergone postgraduate training in tropical medicine at the Swiss Tropical Institute in Basel, Switzerland, and obtained in 1952 the Diploma of Tropical Medicine (D.T.M.);

That I have undergone postgraduate training in public health at the University of Bristol, U.K., and obtained in 1967 the Diploma of Public Health (D.P.H.);

That, as from 1958 until 1988, I have served the World Health Organization as a staff member in the fields of tropical medicine and malaria; between 1978 and 1988 as Chief Medical Officer in charge of global malaria research and *ex officio* Secretary of the Scientific Working Groups on the Chemotherapy and Immunology of Malaria, UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases;

That, as from 1960, I held academic teaching assignments in addition to my WHO assignments, with the Faculty of Medicine, University of Khartoum, Sudan, the University of Tunisia, and the Université Claude Bernard, Lyon, France;

That, in 1988, I have been appointed visiting professor at the University of Vienna, Austria, and the Universiti Sains Malaysia, Penang, and in 1993 at the Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand;

That I am the principal author or coauthor of approximately 100 publications, mainly in the field of malaria and malaria chemotherapy;

That I am a registered member of the medical profession (Medical Board of Central Franconia, Federal Republic of Germany);

That I am a member of the following professional bodies/organizations:

- World Health Organization (WHO) Expert Panel on Malaria
- German Society of Tropical Medicine (Honorary Member)
- Swiss Society of Tropical Medicine and Parasitology (Honorary Member)
- Austrian Society of Tropical Medicine and Parasitology (Council Member)
- Royal Society of Tropical Medicine and Hygiene (U.K.)
- British Society of Public Health
- British Society of Parasitology;

That I am presently working as Visiting Professor (Tropical Medicine) at the Institute for Specific Prophylaxis and Tropical Medicine, Faculty of Medicine, University of Vienna, Austria, and Visiting Professor at the National Centre for Drug Research, Universiti Sains Malaysia, Penang, Malaysia (Tropical Clinical Pharmacology), and as Visiting Professor at the Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand (Tropical Clinical Pharmacology);

That in 1989 the compound artemether was known to me from various publications and my own professional and scientific involvement in the development of artemisinin derivatives;

That in 1989 the compound artemether was known to be poorly soluble in water;

That in 1989 the only envisaged mode of administration of artemether was by the intramuscular route;

That in 1989 the exact dose and regimen of artemether to be administered intramuscularly was not established;

That the Chemical Abstracts reference CA 112(7): 48094s from the review publication by Deng Rongxian, Zhongguo Yiyao Gongye Zazhi 20(8), 372-376 (1989) which reads as follows:

--The recent progress in research on antimalarial drugs in China was reviewed, with 28 refs.. Three new drugs and one preparation have been registered in China since 1985, including artemether, artesunate and qinghasou suppository. New drug naphthoquine and combination of artemether-benflumetol are undergoing Phase II clinical trials. Besides, the combinative application of pyronaridine with other drugs has also been mentioned.--

would have indicated to me that the artemether component of the artemether-benflumetol combination mentioned in this publication was administered intramuscularly;

that the benflumetol component of the artemether-benflumetol combination mentioned in this publication and also the dose and mode of administration of the benflumetol component were unknown to me;

that the mode of administering the artemether-benflumetol combination is undefined in this article;

that based on the disclosure of the abstract the expert expected the artemether component to be administered separately by the intramuscular route, whereas the mode of administration of benflumetol is undefined;

That in the Chinese Journal of Pharmaceuticals 1989, 20(8), the paragraph on page 375, left column, lines 3-13, which relates to artemether and benflumetol and which reads in English translation as follows:

--The combination of artemether and benflumetol in proper proportions has synergistic action and possesses the advantage of both rapid action of artemether and thorough parasitocidal action of benflumetol, and also possibly retards the emergence of single drug resistance and reduces the dosage of single drugs. The toxicity of such combination is only additive.

To explore this, these two individual drugs were first administered simultaneously for treatment of falciparum malaria patients in endemic areas of chloroquine resistance in Hainan Province. The results demonstrated that the parasite clearance rate, fever subsidence rate and cure rate were all better than that of single drugs or chloroquine. The regimen was convenient and safe for use, and has entered clinical trial Phase I.--

that the mode of administering the artemether-benflumetol combination comprises separate administration of the individual components of the artemether-benflumetol combination mentioned;

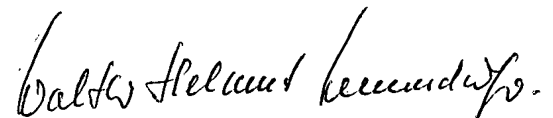
that based on the disclosure of this excerpt the expert also expects the artemether component to be administered separately by the intramuscular route, whereas the mode of administration of benflumetol is undefined;

CONCLUSION

that I conclude from the English translations of the references above that the disclosure according to Chemical Abstracts reference CA 112(7): 48094s and the excerpt from the Chinese Journal of Pharmaceuticals 1989, 20(8), page 375, left column, lines 3-13, which relates to artemether and benflumetol, is non-enabling to the expert with respect to an individual oral dosage form containing effective amounts of both combined antimalarial agents artemether and benflumetol;

The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

Signed at Vienna, Austria, this 31st day of July 1994



Walther H. Wernsdorfer